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Sublingual immunotherapy of atopic dermatitis in mite-sensitized patients: a multi-centre, randomized, double-blind, placebo-controlled study

Lunfei Liu^{a,b}, Jisu Chen^a, Jinhua Xu^c, Qinqing Yang^c, Chaoying Gu^c, Chunya Ni^c, Linfeng Li^d, Xueyan Lu^d, Zhirong Yao^e, Jianfeng Tao^e, Yifeng Guo^e, Hong Fang^f, Yingguo Ding^f, Qihong Qian^g, Naihui Zhou^g, Miaomiao Wang^g, Danqi Deng^h, Hong Xie^h, Shenqiu Liⁱ, Yongchu Huangⁱ, Naiqing Zhao^j and Min Zheng^a

^aDepartment of Dermatology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; ^bDepartment of Dermatology, The Fourth Affiliated Hospital, Zhejiang University School of Medicine, Yiwu, China; ^cDepartment of Dermatology, Huashan Hospital Affiliated to Fudan University, Shanghai, China; ^dDepartment of Dermatology, Peking University Third Hospital, Beijing, China; ^eDepartment of Dermatology, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; ^fDepartment of Dermatology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; ^gDepartment of Dermatology, The First Affiliated Hospital of Soochow University, Suzhou, China; ^hDepartment of Dermatology, The Second Affiliated Hospital of Kunming Medical University, Kunming, China; ⁱDepartment of Dermatology, Tongji Hospital, Tongji Medical College of Huazhong University of Science & Technology, Wuhan, China; ^jFudan School of Public Health, Shanghai, China

ABSTRACT

Allergen-specific immunotherapy is widely used for allergic rhinitis and asthma treatment worldwide. This study explored the efficacy and safety of sublingual immunotherapy (SLIT) with the extracts of *Dermatophagoides Farinae* (*D. farinae* Drops) on house dust mites (HDM)-induced atopic dermatitis (AD). 239 patients with HDM-induced AD were recruited and exposure to a multi-centre, randomized, double-blind, and placebo-controlled clinical trials for 36 weeks, which were randomly divided into placebo and sublingual *D. farinae* Drops groups (high-dose, medium-dose and low-dose), respectively. Statistical analysis was performed in three groups: Full Analysis Set, Per Protocol Set and Safety Set. 48 cases have withdrawn from the study before the end of study. As primary outcomes, significant decreases in scoring atopic dermatitis and total medication score were showed in medium-dose and high-dose *D. farinae* Drops groups. In the sixth visit, the skin lesion area showed a statistically significant difference between high-dose/medium-dose *D. farinae* Drops group and placebo group ($p < .05$). Most adverse events are slight, and no life-threatening adverse drug reaction happened. Our research demonstrates the beneficial effect of SLIT with high or medium dose *D. farinae* Drops on AD, and the treatment was well tolerated.

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Introduction

Atopic dermatitis (AD) is a chronic and relapsing inflammatory skin disease with highly intractable pruritus [1]. Almost 10–20% of children and 1–3% of adults suffer from AD worldwide [2]. The main clinical symptoms of AD are pruritic, eczematous, erythematous and skin lesions with serous exudate or crusts [3]. More seriously, about half of the patients with severe AD will get asthma and about two-thirds of them will develop allergic rhinitis [4]. AD can be divided into two categories: intrinsic AD and extrinsic AD [5]. Extrinsic AD accounts for ~80% of all cases, which shows sensitivity to the environmental allergens, such as house dust mite (HDM), pollen and so on [6]. Allergens, like HDM and pollen, can through skin barrier or respiratory tract, promote the polarization of T helper type 2 cells, elevate the sensitization of specific IgE in serum and aggravate the symptoms of AD [7].

Allergen-specific immunotherapy (ASIT) is recognized as a highly effective practice in the treatment of AD, including in the therapy of natural allergens-caused allergic diseases [8,9]. The rationale of ASIT is lifting the tolerance of patients to the specific allergen by gradually increasing the dose administration of allergen [10]. Its beneficial clinical effects have been demonstrated in the treatment of allergic asthma, atopic rhinitis and hymenoptera allergy [11–13]. In generally, ASIT includes subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) [14]. Due to its higher safety and lower compliance, SLIT has been recommended by the World Allergy Organization (WAO) as an alternative to SCIT for patients with allergic rhinitis and asthma [15].

As a major allergen, HDM can be found worldwide where human beings lives and contains a number of mites, such as *Dermatophagoides farinae*, *Dermatophagoides microceras*, *Dermatophagoides pteronyssinus* and *Euroglyphus maynei* [16].

CONTACT Min Zheng  minz@zju.edu.cn  Department of Dermatology, The Second Affiliated Hospital, Zhejiang University School of Medicine, No. 88, Jiefang Road, Hangzhou 310009, China

*Lunfei Liu and Jisu Chen co-first authors.

SLIT with standardized extracts of *D. farinae* (*D. farinae* Drops) has been applied currently in Chinese clinical II phase practice [17]. Qin et al. proved that SLIT with *D. farinae* Drops could reduce the need of patients with AD for medicine [17]. In this study, we want to further explore the efficacy and safety of SLIT with *D. farinae* Drops on patients with HDM-induced AD. Moreover, this study will provide a clinical basis for design and drug administration of the clinical phase III trial.

Materials and methods

Study design

The study was a clinical phase II, multi-centre, randomized, double-blind, and placebo-controlled trial with 4 parallel groups. Eligible patients were randomly divided into four groups, placebo control group, high-dose *D. farinae* Drops group, medium-dose *D. farinae* Drops group and low-dose *D. farinae* Drops group averagely using a computer-based randomization program (Figure 1(a)). After randomization, patients were assigned to receive relevant treatment for 36 weeks, and regularly received follow-ups, which consist of visit 1–6 in 0, 4, 10, 16, 24 and 36 weeks, respectively. In each visit, diary cards (containing whether take medicine as required) were retrieved, scoring atopic dermatitis (SCORAD) [18], medicine use score (whether use Levocetirizine Hydrochloride Tablets, Mometasone Furoate Cream, Mupirocin Ointment or Clarithromycin Tablets to relieve clinical symptoms), self-evaluation of patients and adverse events (AE) were recorded. In visit 1 and 6, patients were given a completed medical examination, including physical examination and laboratory test.

This study was approved by the Ethics Committee of The Second Affiliated Hospital, Zhejiang University School of Medicine and registered at clinicaltrials.gov (NCT01471119). This study has got IRB approval from all the clinical centres. Written informed consents were obtained from all participants before any protocol-specific procedures were undertaken.

Patients

A total of 239 patients were recruited from October 2011 to February 2014 in The Second Affiliated Hospital, Zhejiang University School of Medicine (48 cases), Huashan Hospital Affiliated to Fudan University (40 cases), Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (40 cases), Peking University Third Hospital (44 cases), Tongji Hospital, Tongji Medical College of Huazhong University of Science & Technology (12 cases), The First Affiliated Hospital of Soochow University (20 cases), The First Affiliated Hospital, Zhejiang University School of Medicine (23 cases) and The Second Affiliated Hospital of Kunming Medical University (12 cases) for clinical trial. Main inclusion criteria include: (1) 18 to 60 years old; (2) $10 \leq \text{SOCRAD} \leq 40$; (3) positive skin prick test results (histamine equivalent or above ++) to *D. farinae* stimulation. Main exclusion criteria include: (1) Patients showing higher skin prick test reaction

to other allergens rather than *D. farinae*, and skin prick test results to these allergens showed above ++++; (2) had received immunotherapy for dust mite in the preceding 3 years; (3) had clinically relevant history of immunosuppressive diseases (such as: history of HIV affection, history of malignancy), autoimmune disease or phthisis; (4) had received UV therapy or systemic treatment with glucocorticoids, leukotriene antagonists or immune-suppressor in the preceding 4 weeks; (5) asthma patients who needed a regular use of glucocorticoids and/or β_2 -adrenoceptor.

Procedures

Eligible patients received sublingual *D. farinae* Drops or placebo (only containing glycerin and saline). *D. farinae* Drops (Nos. 1–5 containing 1, 10, 100, 333 and 1000 $\mu\text{g/ml}$ extracts of *D. Farinae*, respectively, in glycerinated saline) were kindly provided by Zhejiang Wolwo Bio-pharmaceutical Co., Ltd. (Zhejiang, China). Treatment was conducted by two phases: up-dosing phase (1st–10th weeks) and maintenance phase (11th–36th weeks). In up-doing phase, patients received low to high dose of sublingual *D. farinae* Drops or placebo treatment. The specific information on drug dosage in up-doing phase is shown in Table 1. From 11th to 36th weeks, patients took a high dose of sublingual *D. farinae* Drops or placebo daily as a maintenance dose.

In addition, patients can use some concomitant drugs, including Mometasone Furoate Cream, Levocetirizine Hydrochloride Tablets, Mupirocin Ointment or Clarithromycin Tablets to relieve clinical symptoms, such as erythema, pimples or infiltration during the trial. The use of any concomitant drugs during the trial was recorded, and the total amount of concomitant drugs use of each patient was counted for evaluation. The use of medicine count 1 point for each dose of Levocetirizine Hydrochloride Tablets, Mometasone Furoate Cream, Mupirocin Ointment or Clarithromycin Tablets. All patients were instructed to use a daily card to record every consumption of *D. farinae* Drops, medicine for relieve clinical symptoms or AE during the trial.

Assessment of efficacy

The therapeutic efficacy of SLIT with *D. farinae* Drops was assessed using SCORAD index, the use of concomitant drugs to relieve clinical symptoms in maintenance phase, the dermatology life quality index (DLQI) and the skin lesion area. The SCORAD index was recorded in each follow-up. The reduction ratio of SCORAD index was calculated by the score decrease from baselines to each follow-up.

Assessment of safety

Safety of SLIT with *D. farinae* Drops was evaluated by AE and general clinical laboratory evaluations. AE included death, life-threatening, hospitalization, disability, low work efficacy and deformity. General clinical laboratory evaluations included blood routine, urine routine, liver function, renal function and a urine pregnancy test.

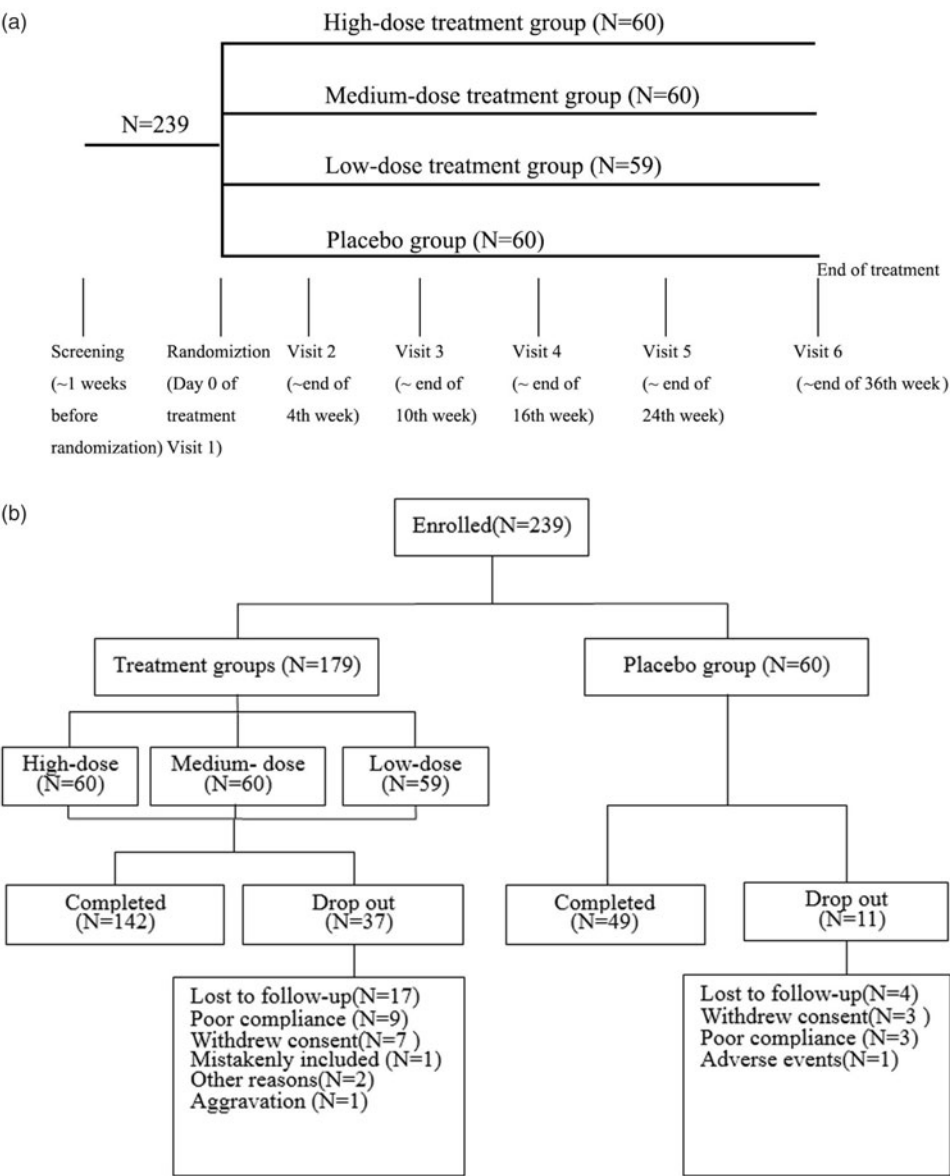


Figure 1. Study design diagram (a) and basic information of withdraw (b).

Table 1. SLIT Dosing schedule.

	Week	Drug no.	First day (drop)	Second day (drop)	Third day (drop)	Fourth day (drop)	Fifth day (drop)	Sixth day (drop)	Seventh day (drop)
Up-dosing phase	1	1	1	1	2	2	3	3	4
	2	1	4	6	6	8	8	10	10
	3	2	1	1	2	2	3	3	4
	4	2	4	6	6	8	8	10	10
	5	3	1	1	2	2	3	3	4
	6	3	4	6	6	8	8	10	10
	7–8	4				3			
	9–10	4/5 ^a				3 ^a			
Maintenance phase	11–36	4/5 ^a				3 ^a			

^aIn the low-dose group, maintenance dose was three drops of No. 4 *D. farinae* Drops. In the medium-dose group, maintenance dose was one drop of No. 5 *D. farinae* Drops and two drops placebo. In the high-dose group, maintenance dose was two drops of *D. farinae* drops and one drop placebo. In the placebo group, patients received same dose placebo as those in SLIT groups at the same time of therapy.

Statistical analysis

Statistical analysis was performed in three groups: Full Analysis Set (FAS), Per Protocol Set (PPS) and Safety Set (SS). FAS included all the patients who had received at least one-time SLIT with *D. farinae* Drops, and could provide at least

one day's diary record. PPS included all the patients with good compliance (received more than 70% SLIT with *D. farinae* Drops of total SLIT with *D. farinae* Drops) and completed all the diary record. FAS and PPS were used for efficacy assessment. SS included all the patients who had received at

least one-time SLIT with *D. farinae* Drops, which was used for safety assessment.

Two-tailed tests were used for statistical analysis with a significant level of 0.05. Qualitative data were evaluated by χ^2 test. Ordinal categorical variables were evaluated by CMH χ^2 test. Quantitative differences among multi-groups were evaluated by one-way analysis of variance or non-parametric test. Clinical efficacy index were evaluated by covariance analysis. Intro-group comparisons were evaluated by *t*-test or sign-rank test.

Results

As shown in Tables 2 and 3, patients in four groups were well balanced in demographics and baseline disease characteristics, as well as the results of skin prick test with various allergens.

A total of 48 cases have withdrawn from the study before the end of study (Figure 1(b)). There are 11 cases in placebo group, 10 cases in high-dose *D. farinae* Drops group, 14 cases in medium-dose *D. farinae* Drops group and 13 cases in low-dose *D. farinae* Drops group. There were no significant differences in withdraw rates between the placebo group and *D. farinae* Drops groups.

Primary efficacy endpoints

Scorad

226 cases were included in FAS, and 193 cases were included in PPS. The SCORAD index of the placebo group and *D. farinae* Drops groups were recorded in every visit during the trail. Results in Figure 2 displayed that the SCORAD indexes were both decreased in the placebo group and *D. farinae* Drops groups. Due to the 4th visit was the first follow-up patients entered into the maintenance phase, and the 6th visit was the last one, we paid attention to the data of these two groups. The results showed that *D. farinae* Drops treatment groups had lower SCORAD indexes in FAS, compared to the placebo group, especially in high-dose and medium-dose *D. farinae* Drops groups ($p < .05$). In the 4th visit, the SCORAD index in PPS was also significantly decreased in high-dose and medium-dose *D. farinae* Drops groups, relative to the placebo group ($p < .05$).

Clinical efficacy rate was evaluated by the percentage of cure and the change of marked effect during the whole treatment phase. The cure, marked effect, improvement, and ineffectiveness were defined by the reduction ratio of SCORAD index after 36th week sublingual *D. farinae* Drops treatment compared to baseline. Compared to a 38.00% (in FAS and PPS) clinical efficacy rate in placebo group,

Table 2. Baseline characteristics of the patients.

	Placebo	SLIT			<i>p</i> -Value
		High-dose	Medium-dose	Low-dose	
Patients enrolled	57	60	55	54	
Age (%)	30.3 (10.4)	31.5 (11.3)	31.4 (11.0)	33.0 (10.7)	.534
Male (%)	29 (54.72)	26 (49.06)	23 (42.59)	31 (60.78)	.168
Weight (%)	60.9 (11.3)	62.7 (11.6)	62.3 (11.4)	63.6 (11.0)	.619
Allergic conjunctivitis (%)	5 (8.77)	4 (6.67)	7 (12.73)	3 (5.56)	.580
Allergic asthma (%)	16 (28.07)	12 (20.00)	15 (27.27)	13 (24.07)	.738
Allergic rhinitis (%)	40 (70.18)	46 (76.67)	39 (70.91)	38 (70.37)	.838
Food allergy (%)	10 (17.54)	7 (11.67)	4 (7.27)	7 (12.96)	.429
Drug allergy (%)	9 (15.79)	3 (5.00)	6 (10.91)	7 (12.96)	.291
SCORAD (%)	32.7 (10.3)	34.0 (9.4)	34.1 (9.6)	35.3 (11.4)	.715
DLQI (%)	11.6 (5.0)	11.8 (6.3)	10.6 (5.0)	11.4 (5.7)	.660
Lesion area score (%)	12.9 (13.1)	11.5 (9.6)	11.6 (9.8)	13.9 (12.8)	.405
Itching (%)	9.3 (4.8)	9.0 (3.9)	10.2 (4.5)	9.1 (4.6)	.460

Table 3. Baseline skin prick test results.

	Placebo	SLIT			<i>p</i> -Value
		High-dose	Medium-dose	Low-dose	
Dermatophagoides farinae (%)					
++	11 (19.30)	9 (15.00)	11 (20.00)	10 (18.52)	.597
+++	22 (38.60)	21 (35.00)	21 (38.18)	13 (24.07)	
++++	24 (42.11)	30 (50.00)	23 (41.82)	31 (57.41)	
Dermatophagoides pteronyssinus (%)					
+	3 (5.26)	0 (0.00)	2 (3.64)	1 (1.85)	.523
++	12 (21.05)	9 (15.00)	10 (18.18)	9 (16.67)	
+++	17 (29.82)	21 (35.00)	18 (32.73)	11 (20.37)	
++++	23 (40.35)	28 (46.67)	22 (40.00)	27 (50.00)	
Cat dander negative (%)	50 (87.72)	53 (88.33)	48 (87.27)	47 (87.04)	.693
Dog dander negative (%)	51 (89.47)	56 (93.33)	53 (96.36)	50 (92.59)	.615
German cockroach negative (%)	46 (80.70)	55 (91.67)	50 (90.91)	53 (98.15)	.244
Artemisia pollen negative (%)	46 (80.70)	52 (86.67)	47 (85.45)	44 (81.48)	.00890**
Platanus pollen negative (%)	52 (91.23)	56 (93.33)	53 (96.36)	49 (90.74)	.661
Penicillium negative (%)	54 (94.74)	59 (98.33)	52 (94.55)	53 (98.15)	.433
Milk negative (%)	55 (96.49)	58 (96.67)	54 (98.18)	51 (94.44)	.191
Peanut negative (%)	57 (100.0)	56 (93.33)	55 (100.0)	53 (98.15)	.107
Egg yolk negative (%)	57 (100.0)	60 (100.0)	54 (98.18)	52 (96.30)	.495
Egg white negative (%)	55 (96.49)	59 (98.33)	54 (98.18)	52 (96.30)	.527

**Difference in the proportion of patients allergic to Artemisia pollen at baseline.

D. farinae Drops treatment groups showed higher rates (Table 4). In high-dose *D. farinae* Drops treatment group and medium-dose *D. farinae* Drops treatment group, the efficacy rate reached to 56.00 and 58.70%, respectively.

Pharmacotherapy medication score

Use of concomitant drugs to relieve clinical symptoms in the maintenance phase (11th to 36th weeks) was evaluated by medication score. Figure 3(a,b) shows that both *D. farinae* Drops treatment groups and the placebo group showed an increase in total medication score from fourth to sixth follow-up. As a major therapeutic medicine for AD, the reduction of glucocorticoids dosage could directly reflect the efficacy of immunotherapy. Thus, the single topical glucocorticoids medication score (at pre-defined targeted area) was compared. From fourth to sixth follow-up, the use of glucocorticoids in the placebo and the low-dose group were increased, while the use of glucocorticoids in the high-dose and medium-dose group still remained at relatively low levels (Figure 3(c,d)).

Secondary efficacy endpoints

Skin lesion area

Skin lesion area was scored over the 36-weeks' treatment. The skin lesion areas were both decreased in *D. farinae* Drops treatment groups and the placebo group. High-dose and medium-dose group displayed a higher decrease in skin lesion areas than the placebo group (Figure 4). In the sixth

follow-up, the differences among high-dose *D. farinae* Drops and placebo group, as well as medium-dose *D. farinae* Drops and placebo group were statistically significant ($p < .05$).

Dermatology life quality index (DLQI)

DLQI was used to evaluate whether the AD symptoms could affect the daily life of patients. DLQI was recorded during the whole 36-weeks treatment. Compared to the baseline, both the placebo group and *D. farinae* Drops groups had a decrease in DLQI (Figure 5). The decrease of DLQI is highest in medium-dose *D. farinae* Drops group, followed by high-dose *D. farinae* Drops group, then low-dose *D. farinae* Drops group and placebo group.

Safety assessment

231 patients were included in SS for safety assessment. There were 41 patients who reported adverse drug reaction (ADR), 85 cases in total. Among them, 19 patients (33 cases) belonged to high-dose *D. farinae* Drops group, 9 patients (24 cases) belonged to medium-dose *D. farinae* Drops group, 6 patients (13 cases) belonged to low-dose *D. farinae* Drops group and 7 patients (15 cases) belonged to the placebo group (Table 5). The difference in number is statistically significant ($p < .05$).

Wherein, 74 cases were mild ADR, 6 cases were moderate ADR, and 5 cases were serious ADR (Table 6). Serious ADR included swelling in tough and lips (three cases, in the medium-dose group), throat pain (one case, in high-dose

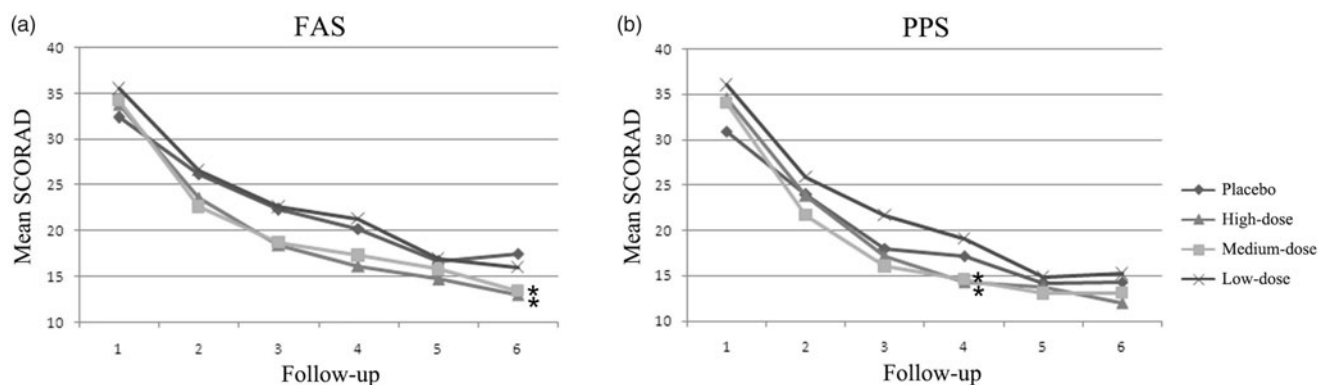


Figure 2. Mean SCORAD over 36-weeks' treatment period. (a) Mean SCORAD in FAS; (b) Mean SCORAD in PPS. * $p < .05$.

Table 4. Clinical efficacy rate.

	FAS (N = 226)				PPS (N = 193)			
	Placebo	High-dose	Medium-dose	Low-dose	Placebo	High-dose	Medium-dose	Low-dose
N (missing)	50 (7)	50 (10)	46 (9)	47 (7)	50 (0)	50 (0)	46 (0)	47 (0)
Cure	9	9	7	3	9	9	7	3
Marked effect	10	19	20	18	10	19	20	18
Improvement	20	17	13	20	20	17	13	20
Ineffective	11	5	6	6	11	5	6	6
Clinical efficacy rate ^a	38.00%	56.00%	58.70%	44.68%	38.00%	56.00%	58.70%	44.68%
p-Value			.124				.124	

^aClinical efficacy rate = (Cure + Marked effect)/(Cure + Marked effect + improvement + ineffective) $\times$ 100. Cure, marked effect, improvement, ineffective is defined by SCORAD reduction ratio = (SCORAD in first follow-up – SCORAD in sixth follow-up)/(SCORAD in first follow-up) $\times$ 100. Cure: SCORAD reduction ratio $\geq$ 90%. Marked effect: SCORAD reduction ratio $\geq$ 60%, $<$ 90%. Improvement: SCORAD reduction ratio $\geq$ 20%, $<$ 60%. Ineffective: SCORAD reduction ratio $<$ 20% or aggregate.

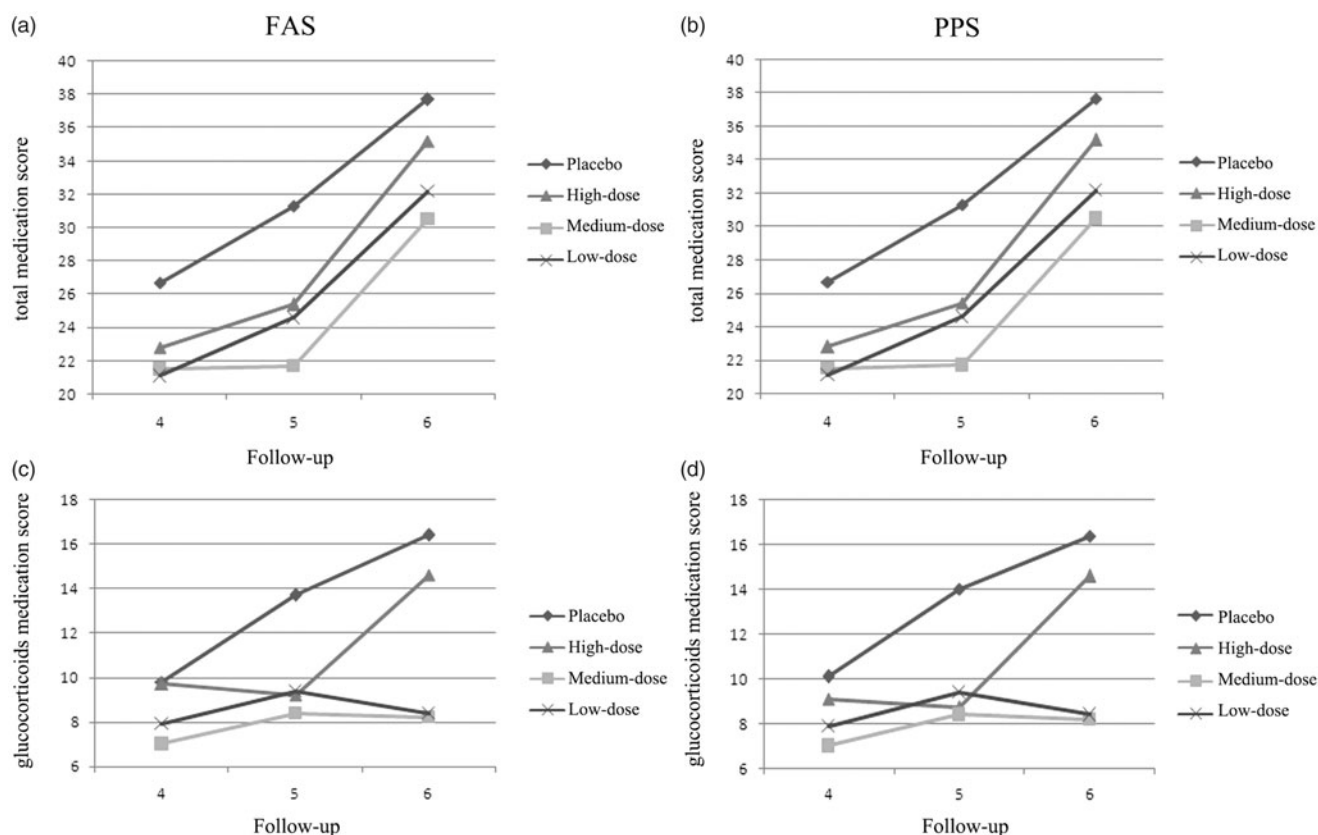


Figure 3. Mean medication score from fourth to sixth follow-up. Medication score was calculated in every follow-up by days of concomitant drugs use. Every single day use of one kind of concomitant drug represented one point. (a) Mean total medication score in FAS. (b) Mean total medication score in PPS. (c) Mean topical glucocorticoids medication score in FAS. (d) Mean topical glucocorticoids medication score in PPS.

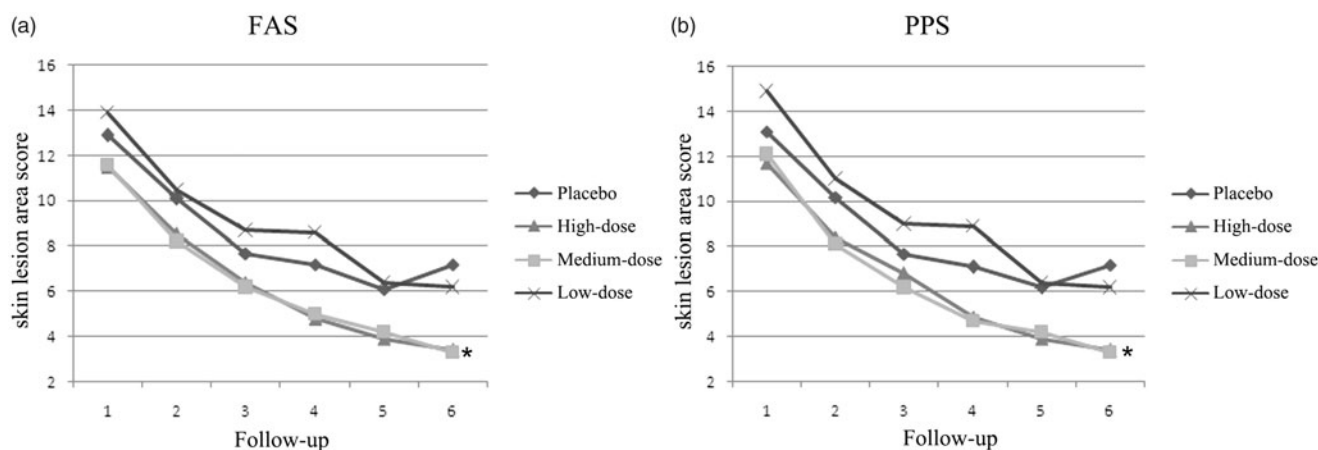


Figure 4. Skin lesion area score from first to sixth follow-up. (a) Skin lesion area score in FAS. (b) Skin lesion area score in PPS. * $p < .05$.

group), and diarrhoea (one case, in high-dose group). None of these five cases dropped out from the study. The mostly occurred ADR were swelling, itching, or numb in mouth, tough, or lips ($N=24$). Most of this kind of ADR was mild and did not need treatment or dose adjustment. No differences in clinical laboratory evaluations and vital signs were observed.

Discussion

Since Scadding G.K. firstly reported the randomized, double-blind, placebo-controlled parallel group clinical trial about

SLIT in 1985 [19], SLIT has been widely used in adults and children for the treatment of AD. An increasing number of reports provide evidence that SLIT is effective in allergic rhinitis and asthma treatment [11,12]. Until now, a few clinical trials concerning SLIT to AD have been reported [20,21]. In 2016, H. H. Tam et al [22] reported a Cochrane systematic review about SLIT for the treatment of atopic eczema, which analyzed 12 eligible trials with 733 subjects. High safety is proved by these trials. In terms of efficacy, two trials showed a significant difference in primary outcomes, while three trials showed no significance. Unfortunately, due to a high statistical heterogeneity, this review is not able to conclude a firm

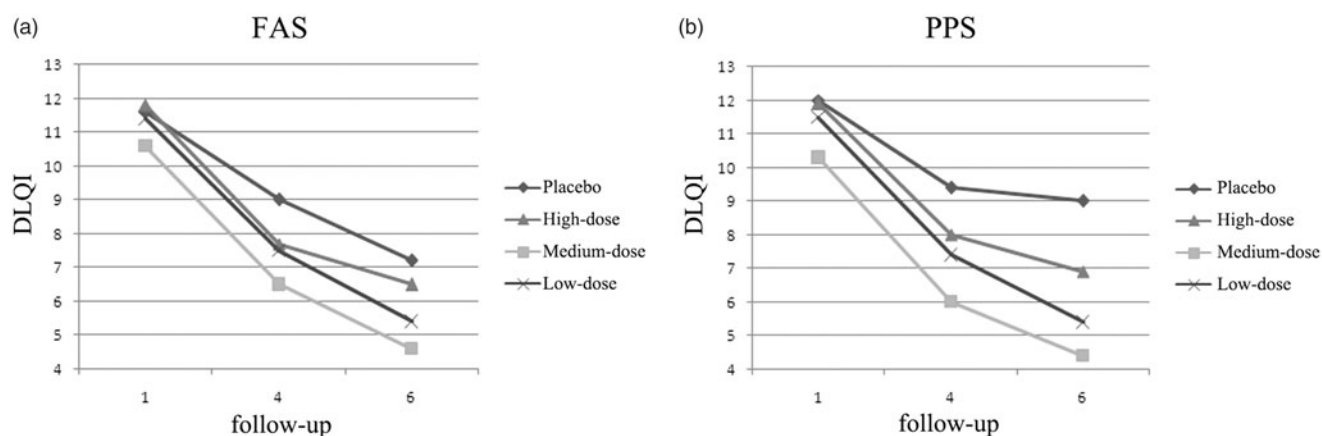


Figure 5. Dermatology life quality index (DLQI). (a) DLQI in first (baseline), fourth and sixth follow-ups in FAS. (b) DLQI in first (baseline), fourth and sixth follow-ups in PPS.

Table 5. Incidence of adverse drug reaction.

	N	No. of subjects with ADR	No. of cases with ADR
Total	231	41	85
Placebo	58	7	15
High-dose	60	19	33
Medium-dose	56	9	24
Low-dose	57	6	13
p-Value		.0100	.0127

Table 6. Number and severity of adverse drug reaction.

Severity	Placebo	High-dose	Medium-dose	Low-dose	Total
Mild, N (%)	15 (20.27%)	30 (40.54%)	16 (21.62%)	13 (17.57%)	74
Moderate, N (%)	0 (0.00%)	1 (16.67%)	5 (83.33%)	0 (0.00%)	6
Serious, N (%)	0 (0.00%)	2 (40.00%)	3 (60.00%)	0 (0.00%)	5

report whether ASIT is efficient in the treatment of AD. More clinical trials are still needed to further assess whether ASIT has a beneficial effect on AD.

Herein, we further tested the efficacy and safety of SLIT with *D. farinae* Drops on patients with HDM-induced AD. As a dosage exploratory clinical trial, we reported a certain decrease in SCORAD, concomitant drugs use, skin lesion area, and improvement in DLQI in high and medium-dose *D. farinae* Drops groups, especially in the medium-dose group, which suggests medium-dose *D. farinae* Drops might be the proper dose for treatment. These results suggest a positive response of AD patients to SLIT treatment. However, most of the primary outcomes didn't show statistically significant differences. Further long term clinical trials are needed to further validate the efficacy of SLIT in the treatment of AD.

Pajno et al. conducted an 18-months' randomized, double-blind, placebo-controlled parallel group clinical trial about SLIT to AD with 56 subjects, which indicated that SCORAD started to decrease after 9 months treatment, and showed a significant decline after 18 months treatment [21]. Glover and Atherton conducted a randomized, double-blind clinical trial on immunotherapy to AD among 24 children [23]. They found that there was no statistical significance after 8 months treatment. When the trial continued for another 6 months, the treatment group showed a significant lower score than the placebo group. These findings suggest that a long term for immunotherapy is necessary. In our study, we observed an increase in SCORAD from fifth to sixth follow-up in the

placebo group. We regarded that it was a decline of the placebo effect. With the extension of the treatment period, the placebo effect could be diminished, and the effect of immunotherapy could be more significant. Thus, a significant improvement in a longer term's immunotherapy is expected.

Topical glucocorticoids are the most effective therapeutic drugs to AD [24]. Then, we suppose that the use of topical glucocorticoids can reduce SCORAD during the study, which explains why all the placebo and treatment groups showed a reduction in SCORAD. It also indicates that the reduction use of topical glucocorticoids could directly reflect the efficacy of SLIT. We reported a lower topical glucocorticoids medication score in all three *D. farinae* Drops treatment groups, especially in medium-dose *D. farinae* Drops group, which indicated that SLIT may reduce the use of therapeutic drugs to AD.

During the immunotherapy, patients may experience a lower risk of arising AD symptoms again [25]. On the other aspect, patients also can use medicine to control the clinical symptoms during SLIT. By this way, patients were expected to have a lower possibility in AD relapse. According to a subgroup analysis evaluating the period for not using topical glucocorticoids after $\text{IGA} \leq 2$, In this clinical trial, we set control over the use of glucocorticoids. When $\text{IGA} \geq 3$, mometasone furoate cream could be used consistently until when $\text{IGA} \leq 1$. However, most patients failed to conduct this medication rule because of relative low compliance. This may help to explain why the difference of topical glucocorticoids medication score was not statistically significant.

In this clinical trial, no serious systemic AE was happened, which proved that SLIT with *D. farinae* Drops is well tolerated to adult patients. Moreover, we found that a higher incidence rate of ADR in the high-dose group, and investigators speculate that a relative high-dose allergen may promote the allergic reaction in patients, which result in the AE. Therefore, it hints that an appropriate dose in the maintenance phase is important for safety consideration.

Though this clinical trial didn't include children as clinical trial subjects, the well-tolerated of SLIT to children has been firmly testified in many previous clinical trials and found that no life-threatening AE happened in a clinical trial of SLIT to children [26].

To conclude, this research investigated the efficacy and safety of SLIT with *D. farinae* Drops on patients with HDM-induced AD. We found that SLIT with an appropriate dosage of *D. farinae* Drops could reduce the SCORAD, lower the use of concomitant drugs and improve the DLQI. A low dosage of *D. farinae* Drops cannot have good efficacy, while the excessive dosage of *D. farinae* Drops may cause adverse reactions and influence the safety of the treatment. The findings of our research provide experimental and clinical basis for clinical phase III trial of SLIT with *D. farinae* Drops on patients with HDM-induced AD. In the clinical phase III trial, we should prolong the time of study and choose a more suitable *D. farinae* Drops dosage.

Disclosure statement

We declare that we have no personal relationships with other people or organizations that can inappropriately influence our work. There is no professional or other personal interest that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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